3. The applicant requests that page 3, paragraph [0009] be appended by the following sentence: Maleic acid hydrazide, or Malazide was patented by U.S. Rubber Co., U. S. Patent 2,575,954,1951.

4. The applicant requests that page 4, paragraph [0013] be appended by the following sentence: Isoniazid or Isonicotinic acid hydrazide was patented in 1958, by Distillers Co.,U. S. Patent 2,830,994,1958, and has a therapeutic dose of 1.5 to 2.5 mg per kg body weight by mouth 2 time daily with pridoxine 50 mg to offset neurotoxicity according to Cutting's Handbook of Pharmacology 6th ed., p.40 (1979).

5. Applicant requests page 5, paragraph [0018], first sentence be replaced by the following sentence: It is noteworthy to recognize that a 50 year history of such hydrazide substrate drug use has existed without any untoward effects evolving from such long term use.

6. The applicant requests that page 5, paragraph [0018] be appended by the following sentence: The MAOI drug Iproniazid (Marsilid) has a therapeutic dose of 50-150 mg daily by mouth and has 1760 mg/kg lethal dose for mice as listed by Psychotropic Drugs and Related Compounds, Public Health Service Publications No.1589 (1967).

7. Applicant requests page 6, paragraph [0021], last sentence be replaced by the following sentence: The Morboran antiviral product has a therapeutic dose of 1500-3000 mg daily by mouth as addressed in Cutting's Handbook of Pharmacology 6th ed., p.125 (1979).

8. The applicant requests that page 7, paragraph [0024], be replaced with the proper title:
[0024] Hybrid Protease Inhibitors having Enzyme Type Selectivity

9. The applicant requests that page 7, paragraph [0025], be replaced by the following paragraph:
[0025] The prior art hydrazide discoveries of the 1950's era listed above were simple pro drug molecules with the exception of the discovery that provided Marboran, the hydrazide having very high antiviral efficacy. Then about 1990 a different type hydrazide appeared having hybrid molecular structures that provides selective protease inhibitor functions. Such class of compounds negate the prodrug action found in the simple hydrazide molecules of the 1950's era by nature of their complex hybrid molecular structures that provides action that targets the selected protease enzyme so as to window the hydrazide

cleavage targeting action to the particular type protease enzyme molecule it inhibits. Such mechanism is exhibited by the cathepsin K protease inhibitors disclosed by WO 97/16433, WO 98/48799, and WO 99/66925. The WO 97/16433, document on page 6 indicates that a structurally diverse variety of cathepsin K inhibitors already exist but are beset with metabolic side effects too severe for medical uses due to cytotoxicity, poor solubility, and over rapid plasma clearance. As such the patents disclose efforts to undertake the organic synthesis and evaluation of a myriad of different molecules types because some may provide, "selective inhibition of cathepsin K that may provide an effective treatment for diseases of excessive bone loss," as stated on page 3 of WO 97/16433. Cathepsin K has a systemic use to metabolize a protein product that mediates a bone loss process while the bone is in a state of flux being disassembled and reassembled as occurs with normal bone growth. The purpose of the cathepsin K inhibitor seems to be to block the bone disassembly side of the process while the rebuilding phase continues uninhibited thus providing a purpose to stop bone loss. Such cathepsin K and other hydrazides that have a protease enzyme selective feature are unrelated to the MAOI hydrazide by type, mechanism, method, use, and purpose.

10. The applicant requests that page 8, paragraph [0030], be replaced by the following paragraph:
[0030] The present invention has reduced to practice for medical purposes the prior art discoveries that have provide working examples of the same mechanism used by the present invention. The first working example was Malazide introduced in 1949, as a plant growth inhibitor which shutdown cell protein biosynthesis for purposes to inhibit cell division or growth. Then in 1952, Iproniazid was used to shutdown ongoing cell protein biosynthesis for tuberculostatic purposes that rendered the bacilli sterile and static but did not kill them as was the objective. Then about 1953, Iproniazid used such method for antidepressant drug purposes by shutting down ongoing protein biosynthesis as a means to inhibit oxidase proteins in CNS cells. And about that same time in 1953, Marboran supplied a hydrazide substrate targeted by protease cleavage in cells that hosted smallpox, polio, and other viral infections which terminated the viral activity. Then some time later Aldrich Chemical Company began supplying Iproniazid for a third new purpose as a preservative for tissue homogenates because it did not kill live cells or bacterial contaminates but shutdown protein producing capability that rendered such cells sterile and static which preserved the integrity of the homogenate. Such long chain of evidenced use to shutdown protein production in cells to provide many different novel purpose for such mechanism is unprecedented and yet provides another new purpose for MAOI hydrazides as provided by this present invention. That new purpose is to shutdown metastatic and abnormal proteins in cells like those that host

cancer, viral, and similar mechanisms, and also used to the shutdown cells innate to infectious microorganisms which provides the principal uses this invention has successfully reduced to practice. However this invention was not the first to use such method for medical disease purposes as the antiviral agent Marboran, as described above, has that distinction. The present invention only provides an improvement over Marboran by eliminating the cytotoxic source of hydrazide used by Marboran which is replaced by the safe and efficacious MAOI type hydrazide.

11. The applicant requests that page 11, paragraph [0042], be appended with the following sentences: The procedure used to prepare Isoniazid follows:- Equivalent molar amounts of the nicotinamide product and the hydrazine product in 3 parts of water are heated under reflux till no more ammonia is evolved. The product is cooled and the nicotinoyl hydrazide product is collected by filtration. The procedure used to prepare Iproniazid is likewise provided as follows: :- Equivalent molar amounts of the nicotinamide isomer product and the isopropyl hydrazine isomer product in 3 parts of water are heated under reflux till no more ammonia is evolved. The product is cooled and the isonicotiic acid 2-isopropyl hydrazide product or related isomer product synthesized is collected by filtration.

12. The applicant requests that page 12, paragraph [0045], be replaced by the following paragraph: **[0045]** On April 2, 2003, the applicant filed a Provisional Patent document, 60/459,694, that provides the concepts, applied uses, and the claims that define the present invention which the applicant claims the benefits to and which also teaches and describes the successful applied uses of this invention. The principal concepts reduced to practice were based on the working hypothesis of paragraphs 5 and 37, which conveys remedial treatment means based on the capabilities of hydrazide as listed in paragraph 6, and which were reduced to practice as pertaining to impromptu occasions when illness befell the applicant. Before any treatment concept was used however a high-level of predictability for the required result was deemed necessary and provided by the recognized similarities and analogous uses having been successfully reduced to practice by the prior art applications. For example the antiviral drug Marboran in 1953 illustrates a serendipitous discovery based on hydrazide which shutdown smallpox, polio, and all other viruses tested but the product had cytotoxic problems which based on the working hypothesis was easily overcome by the present invention by using a nontoxic prodrug hydrazide as Iproniazid to supply the hydrazide substrate. Additionally malic acid hydrazide in 1949, was used to shutdown protein products responsible for cell division and growth and did so in a benign and gentle way that would cause no systemic damages or problems if such hydrazide method had been applied to stop cancer growth and

cell division for human use. And the antibiotic concept is also illustrated in hindsight provided by the hypothesis because hydrazide has been used to preserve tissue homogenate that renders live cells and bacterial contaminants sterile and static without killing the live cells or bacteria in the homogenates. Essentially all prior art operations are explained by the hypothesis which has reveals the new applications like the cancer, viral infections, and antibiotic concepts which are based in science and the arts, and which the present invention has reduced to successful medical practice.

13. The applicant requests that page 12, paragraph [0046] be replaced by the following paragraph:
[0046] The medical value for hydrazide as a disease treatment method pertains in part to three areas of dire public need where cancer, viral disease, and infectious organisms present the greatest threats to human life. Such categories of disease have a common dependance on cells having a capability to provide copious amounts of protein illustrated by: (1) cells that host viral infections and are incessantly active producing viral coat proteins and related products; (2) cells which host cancer or other mutant protein related activity characterized by production of metastatic, abnormal, or aberrant protein products; and (3) cells that are innate to infectious microorganisms and are thus active in providing proteins that are toxic, pain producing, and dangerous in addition to the normal protein production needs as cell division, growth, and proliferation requires. The best mode for medical use in such cases is to shut down protein production which shuts down disease activity by the applied use of a medically safe hydrazide source as the MAOI type hydrazides provides. Such hydrazides are readily targeted by protease cleavage as provided by the protein producing cells which shuts down the protein biosynthesis capability thus rendering such protein producing cells sterile and static As such the hydrazide most used to provide analogous use to shutdown protein producing activity in a rapid, safe, and efficacious manner is isonicotinic acid 2-isopropyl hydrazide which was provided under the name of Iproniazid supplied by Aldrich Chemical of Milwaukee, catalog no.1-1,265-4. And the best mode contemplated for disease treatment in performance of this invention was to follow the same protocol and dosage regimen listed by the manufacture for Iproniazid when used for antidepressant drug purposes. That dose level is about 50 to 150 mg daily which is sufficient to shutdown oxidase protein production that provides the antidepressant purpose provided by Iproniazid, and which therefore is a sufficient dose level needed to shutdown viral coat, cancer metastatic, or the proteins as produced by infectious microorganisms.

14. The applicant requests that page13, paragraph [0049], be appended by the following sentences: Protein production is necessary in every aspect of viral disease activity and any means used to disrupt or inhibit the protein production disrupts and inhibits disease activity. As such a number of protease inhibitors have been produced that interferes with, or that slows down protein biosynthesis for temporary periods, but none have been designed around the irreversible hydrazide substrate method as the present invention provides. Hydrazide use provides an irreversible substrate mechanism which shuts down protein biosynthesis provided by the cells that host viral infection which renders such diseased cells static and sterile that ends disease activity and renders such cells for apoptosis. The MAOI hydrazide method is the preferred antiviral agent as its actions are permanent and irreversible which ends the host cell's disease activity permanently following protease targeting of the hydrazide substrate. The method is applicable for all types of viruses, whereas other types of protease inhibitors are disease specific and reversible, such that a continuing medication need exists to keep the disease under tolerable conditions.

15. The applicant requests that page 13, paragraph [0050] be replaced by the following paragraph: **[0050]** The 60/649,694 document discloses antiviral use based on the MAOI hydrazide drug Iproniazid, and in particular describes how HIV illnesses suffered by the applicant was successfully treated by the MAOI hydrazide method. This illness developed following an eye injury where the applicant received emergency room treatment and was in essence inoculated by HIV while in the emergency room. Such inoculation was followed within 3 or 4 days with a light fever and malaise, and within about 18 months with persistent yeast infections, viral conjunctivitis, increasing malaise, arthritic pains, mental fatigue and many less significant symptoms developed. The condition did not improve or worsen substantially for a lengthy period thereafter until a purple discoloration on the front of the lower legs were noticed to have appeared which is indicative of Kaposi's Sarcoma. Following the realization that full blown AIDS was next in order, the applicant provided a blood sample for testing and was informed that he should seek treatment and have additional testing done. Since no cure is offered for such disease the applicant decided to return to the hydrazide research interest he had worked on years earlier believing Iproniazid ended a bout with influenza and that such had promise whereas current treatment methods had little to offer. As such the applicant prepared to test a number of ideas but began with about 100 mg of iproniazid that shutdown the viral activity for several weeks as was indicated by the disappearance of inflammation of the conjunctiva, improved energy, and relief of joint pain and such like. And after about two weeks the virus did return as evidenced by the reappearance of viral conjunctivitis and former symptoms such that the planned research was then continued to test other treatment schemes and ideas. After that study was

completed the virus was then eradicated in total following a subsequent large dose of Iproniazid which likewise shutdown the case of viral conjunctivitis that coexisted at the time where all symptoms abated and did no return.

16. The applicant requests that page 14, paragraph [0051] be replaced by the following paragraph:
[0051] Such rapid antiviral action and extreme efficacy has only been evidenced by one other invention which was also based on hydrazide and produced under the name of Marboran. The hydrazide method used the same mechanism as the present invention but utilized an unsafe thiosemicarbazone laboratory chemical reagent source to provide the hydrazide substrate as is further described in the prior art section, paragraph 19, and also addressed in Cutting's Handbook of Pharmacology 6th ed., p.125, (1979). Although Marboran evidenced amazing antiviral efficiacy and very rapidly shutdown all viral infections tested, including smallpox, polio, and others viruses, Marboran was a serendipitous discovery based on a toxic laboratory reagent source and the toxic effects remained in the final product and diluted the hydrazide action. In hindsight of the working hypothesis and the understanding it provides on which the present invention is based the Marboran cytotoxic problem could have been overcome in 1953 using Iproniazid that was also available at that time, and which would have provided an exceedingly powerful nontoxic antiviral agent using the MAOI hydrazide source. However the cause of the Marboran cytotoxic problems were never isolated or overcome and was discontinued. The present invention however exceeds Marboran as an antiviral agent by shutting down HIV and influenza amazingly fast at a fraction of the dose level as would be required by Marboran to shutdown smallpox and polio. And most importantly Iproniazid has no toxic effects. The safety of iproniazid as a source of the hydrazide substrate is evidenced by more that 50 years of safe use abroad as an antidepressant drug. As such the present invention constitutes a major improvement over prior art Marboran.

17. The applicant requests that page 15, paragraph [0057] be replaced by the following paragraph:
[0057] Cells that host cancer are incessantly producing cancer related protein products and as such are quickly shutdown by drugs of the MAOI hydrazide class. Such cells must supply protein for cancer cell division and growth, and supply the metastatic protein that envelopes the RNA cancer packet which is in essence the cancer germ. Such RNA packet with its tough protein compliment while still intact are pushed out of the cell to travel to a new receptive host cells where the metastatic packet is invaginated into the new host cell. Then reverse transcription occurs where the RNA cancer code program is converted back into DNA similar to action of an RNA virus where it is then incorporated into cell DNA.

When the new DNA code is activated the cancer program takes control which repeats without ending in recursive fashion where such RNA metastatic packets are continually replicated while the cells undergo cell division that provides a second dimension for disease expansion. Such disease activity makes tremendous demand for protein that renders cancer cells very vulnerable to the hydrazide mechanism. This is because substrate resources are in great demand if not totally depleted by such incessant demand for protein production such that the hydrazide substrate is without competition and immediately becomes targeted by protease cleavage in such host cells when the hydrazide is first introduced into the system which shuts down protease and cell protein production capability which in turn shuts down disease activity in such cell that host cancer. Such action in effect targets the cells that host disease activity and then shuts down protein production capability that renders cells sterile, static, and doomed to apoptosis.

18. The applicant requests that page 15, paragraph [0058] be replaced by the following paragraph:
[0058] The hydrazide anticancer concept was also reduced to practice when an impromptu opportunity appeared when a decade old mole began to metastasize. The growth was about a half inch in diameter located in the center of the applicant's forehead, and had remained stable, symmetrical, and unchanged for years when it began to increase in size, shape, and having mixed pigmentation indicative of malignant melanoma. At such time the applicant began a treatment regimen based on Iproniazid Phosphate at about 100 mg daily for about three or four weeks when the perimeter of the growth began to separate from the skin surface underneath and itch. The applicant would unconsciously pick at the protruding edge as if picking at a scab which served to more quickly separated the neoplastic part at its perimeter where sections were then peeled away. Over a period of days the cancer like neoplasm was removed in total which exposed the epidermal layer that soon took on a normal appearance without any signs of cancerous tissue remaining. A second more benign cancer growth coexisted at the same time the melanoma treatment existed which was of the basal cell carcinoma type which was not very noticeable, bothersome, or believed to be threatening but which also disappeared following the melanoma treatment. Such condition was located below the left eye on the applicant's cheek which was characterized by a hard, gritty, cellular formation where scratching or rubbing the surface would dislodge some of the small hard cells which is a common characteristic of basal cell carcinoma. Although the condition was not apparent or threatening at the time, and has never raised concerns or the idea as providing opportunity for Iproniazid screening as the melanoma cancer did, it was nevertheless inadvertently screened against Iproniazid and had likewise disappeared following soon after the melanoma cancer.

19. The applicant requests that page 15, paragraph [0060] be replaced by the following paragraph:

[0060] The hydrazide drug prevents peptide productions that controls cell division, growth, and proliferation of infectious organisms as bacterial, fungal, protozoal, metazoa, and others. Iproniazid provides a prodrug mechanism that does not react as a drug but does react to protease cleavage action to shutdown protein biosynthesis capability in active protein producing cells. Such mechanism provides a new antibiotic purpose to shutdown the cells innate to dangerous microorganisms that are continually providing protein for cell division, growth, and toxic protein generation. Hydrazide has not been recognized as an antibiotic method probably because conventional antibiotics kill microorganisms which is evidenced by the apoptotic fragments seen by microscopic assay which would suggest to researchers that hydrazides have no antibiotic value because the microorganisms are not killed by it. However the value of antibiotics is not how quickly it kills a microorganisms but how quickly it can render a dangerous microorganism sterile, static, and harmless which is much faster than conventional antibiotics can kill them. It is the toxic and dangerous pain producing poisonous proteins, that makes the comparative difference between a benign acidophilus bacterium and the extremely dangerous anthrax type. However within minutes the rapidly replicating toxin producing anthrax organisms would be rendered sterile, static, and harmless by the hydrazide method and as such would no longer provides a danger to its host or have capability of infecting others. Such new antibiotic concept for hydrazide constitutes the original stand alone antibiotic concept had by the applicant as presented at paragraph 30 of the 60/459,694 provisional patent and is also reflected in the claims b, c, and d. on page 12 of that document. Such antibiotic purpose was first reduced to practice followed a poorly prepared evening meal provided by the applicant consisting of leftovers that was followed with extreme stomach pain and griping, indicative of bacterial gastroenteritis. The condition was quickly remedied after taking a 100 mg dose of Iproniazid with a glass of warm tap water. Within about 5 minutes it was evident that the concept was extremely efficacious and rapid acting as most pain was gone and within about 10 minutes all pain and griping had disappeared in total and did not return.

20. The applicant requests that page 16, paragraph [0061] be replaced by the following paragraph:

[0061] As such hydrazides may not be impressive to kill microorganisms as a conventional antibiotics assay would reveal but it is impressive for purposes to more quickly render such microorganisms sterile, static, and harmless. And if for some reason it would be desired to quickly kill off such sterile and static microorganisms sooner than otherwise would happen when eventual apoptotic or immune system activity provides for such, then such hydrazide method can be used in combination with conventional antibiotics

to increase the benefits of both products synergistically and thus kill the organisms faster. Such combination would also provide an adjuvant purpose which would hold microorganism reproduction and proliferation in check and in essence allow smaller amounts of hydrazide and the conventional antibiotics product to be used to provide the same antibiotic result, and the microorganism would be incapable of developing and passing on antibiotic resistance traits to successive generations. Antibiotic resistant organisms have become a major problem due to world population levels that are increasingly dependent on a limited number of antibiotic drugs. Such problems are exacerbated by the unnecessary and frivolous use of antibiotics in the livestock industry, and such problems caused by abuse of conventional antibiotics would be negated if a MAOI hydrazide substrate drug were prescribed concurrent with antibiotic use, or added to animal antibiotic preparations in minimal amounts, or just added to animal feed at minimum levels as a prophylaxis drug.

21. The applicant requests that page 22, paragraph [0088], be replaced by the following paragraph:
[0088] (a) The acronym "MAOI" means "mono amine oxidase inhibitor" where oxidase is only one of many proteins inhibited by hydrazide when used for antidepressant purposes. (b) The term "irreversible hydrazide substrate" relates to drugs of the MAOI class and hydrazide molecules having capability to shutdown ongoing protein biosynthesis in cells which cannot be repaired or reversed because an operational protease enzyme is required to supply a replacement protease enzyme protein. (c) The term "MAOI hydrazide drug" refers to the hydrazide preparations that have antidepressant use capability as exemplified by iproniazid (Marsilid), isocarboxazid (Marplan), and nialimide (Niamid), which have no cytotoxic effects which provides a new chemotherapeutic or disease treatment purpose re Kirby, 40 USPQ 368. (d) The acronym, "APA" as used in the 60/459,694, document means "active protease arrester" which conveys a lengthy meaning that encompasses actions where the ongoing protease enzyme activity and the ongoing protein biosynthesis activity in cells are shutdown irreversibly by protease cleavage action that targets the hydrazide substrate during the process of protein biosynthesis.

22. The applicant requests that paragraphs [0073] through [0078] be deleted from the Specification.